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Medtronic Inc.

By Juanita D. Traufler Date Dec. 7, 2004
Juanita Traufler

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	: Kenneth B. Stokes Josee Morissette	)
Serial No.	: 09/376,317	)
Filed	: August 18, 1999	) Group Art Unit:) 1632
For	: System and Method for Genetically Treating Cardiac Conduction Disturbance	) Examiner:) Anne Marie S. Wehbe
Docket No.	: P3569.01 Continuation	)

REVISED REPLY UNDER 37 C.F.R. 111 &
REVISED AMENDMENT UNDER 37 C.F.R. 1.121

SUBMITTED REVISED REPLY AND AMENDMENTS IN SUPPORT OF APPLICANTS' REQUEST FOR RECONSIDERATION OF THEIR PETITION OF APRIL 29, 2004

Mail Stop Petitions
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The revised reply and amendments are submitted as part of supporting Applicants' Request for Reconsideration on Applicants' original Petition to Revive Application number US

09/376,317. The submitted Revised Reply and Amendments are based on reviewing the Examiner's Advisory Action (received November 11, 2004) and conversations held with the Examiner on October 5, 2004. Applicants have also submitted with the enclosed documents a Request for Continued Examination (RCE).

The enclosed response is an attempt to put the case in condition for allowance. This response is an attempt to re-address issues originally raised by the Examiner in the mailed office action of December 19, 2001. Applicants also request that the previously submitted Supplemental Information Disclosure Statement on April 29, 2004, be entered. In the alternative, should Applicants not have succeeded in placing the Application in condition for allowance and their supplemental IDS has not been entered, Applicants respectfully request their Request for Continued Examination (RCE) and their request for Reconsideration on their Petition to Revive be supported by the Examiner.

In the Office Action dated December 19, 2001, the Examiner rejected pending claims 1, 4-14, 20-25, 39-42 and 48-50. Applicants respectfully request reconsideration of the above-captioned application under 37 C.F.R. §1.115 in light of the amendments and remarks in this response.

Applicants authorize the office to charge deposit account No. 13-2546, in the name of Medtronic, Inc., the fee under 37 C.F.R. §1.17(c) for their Request for Reconsideration (or for any necessary fees related to their response).

Amendments

Applicants request cancellation, without prejudice, of Claims 1, 4-14, 21-25, 39-42 and 48-50.

Please enter the contained amendments to Claim 20 found in the marked up version of the claims attached herewith.

Explanation of The Amendments

In order to facilitate the Examiner's review and to narrow the issues under consideration, Applicants have cancelled all claims except for Claim 20. In response to the Office Action dated December 19, 2001, Paper No. 11, please enter the amendments contained on the marked up version of Claim 20.

The submitted marked-up version of claim 20 follows standard amendment rules, wherein added text has been underlined and deleted text has been bracketed, and the status of each claim has been indicated. Applicants respectfully request entry of the submitted amendments.

Claim 20 has been amended to add the feature that after the cells are contacted, the cells are transfected or transducted with the vector. Support for adding this feature can be found starting at the second to last paragraph on page 20, and proceeding through to the end of the first paragraph on page 22. Additional support can be found throughout the specification. Support for the mapping catheter means can be found on page 8, lines 1-4; page 15, last 4 lines, and page 16, first full paragraph. Support for the use of the pacing electrode with a pacemaker in conjunction with the delivery catheter can be found on page 12, last paragraph through the first paragraph on page 13; and on page 16, first full paragraph.

II. RESPONSE TO THE REJECTIONS MADE IN THE FINAL OFFICE ACTION

In the communication from the Examiner mailed December 19, 2001, the Examiner maintains rejected claims on the following bases:

Claims 1, 4-14, 20-25, 39-42, and 48-50 were finally rejected under 35 U.S.C. Section 112, first paragraph, for lack of enablement.

Claims 1, 4-14, 20-25, 39-42, and 48-50 stand rejected under 35 U.S.C. 103, as being unpatentable over Mulier et al. (WO 95/05781) in view of Leiden et al. (WO 94/11506) and Kanter et al. (1994).

Response to each of the foregoing rejections is provided below.

Claim Rejections – 35 USC § 112.

Claims 1, 4-14, 20-25, 39-42, and 48-50 stand rejected under 35 U.S.C. Section 112, first paragraph, for lack of enablement. Applicants have presently cancelled all claims except for Claim 20. Claim 20 has been amended.

The Examiner had previously found that the specification did not provide an enabling disclosure for the delivery of therapeutically effective amounts of any conduction protein to cardiac tissues using any genetic material including nucleic acid vectors such that any effect on cardiac conduction is observed. The rejection under 112 was indicated to be based on "how to use" the invention as disclosed in the instant specification. 35 U.S.C. 112, first paragraph.

Applicants respectfully traverse in view of the submitted amendments and arguments. Prosecution is now focused on Claim 20. The examiner rejected the Claims basically on two grounds that the invention is not enabled: (1) methods are essentially inadequate to deliver and transfect/transduct genes to cardiac tissue; and (2) the teachings are inadequate to effectively teach one skilled in the art how to deliver connexins for their intended purpose.

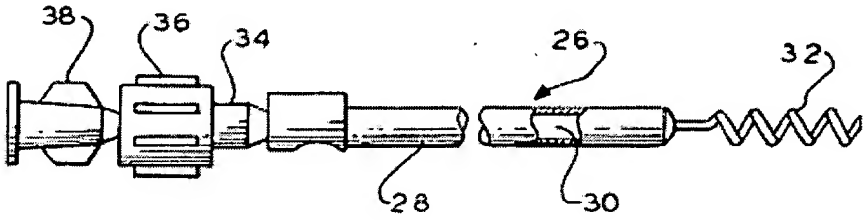
(1) Methods are adequately known in the art to transfect/transduct genes in cardiac tissue.

In regard to the first issue, applicants believe there are presently adequate methods and systems for delivery of genetic agents to the heart. For example, US Patent 5,797,870 (herein also referred to as the '870 patent – submitted in Applicants Supplemental IDS of April 20,

2004), issued 8/25/1998, and corresponds to PCT application, WO 9639830, published 12/19/1996. Issued Claim 1, is as follows:

> 1. A method for delivering a gene therapy agent to epicardial and pericardial tissue of a patient's heart, comprising; providing an elongated intravascular device having a distal tip configured to pierce a wall of the patient's heart; guiding the distal tip of the device into the left ventricle of the patient's heart; piercing the endocardium, the myocardium and the epicardium with the distal tip of the device, said distal tip being located in the pericardial space; introducing the gene therapy agent through the distal tip; and; maintaining the gene therapy agent within the pericardial space for a sufficient period of time. [US 5,797,870 – Claim 1]

Picture of the catheter device from the '870 patent is pictured below:



The US patent office believes in view of the '870 patent that one would, prior to the date of the invention, be able to perform the transfection and transduction methods and procedures claimed and described therein using a helical screw-in tip.

(2) Teachings of the specification are adequate to effectively teach one skilled in the art how to deliver and control connexin expression for its intended purpose.

It has also been indicated there are deficits of the specification in regard to enablement to effectively teach how to deliver and control connexin expression for its intended purposes. For instance, the examiner indicates the specification only provides "prophetic examples for the isolation and purification of connexin cDNA into plasmids and adenoviral vectors", and "fails to provide any guidance as to the identity, sequence, or biological properties of any conduction proteins **OTHER THAN the connexin family members listed above (Cx40, Cx43, Cx45).**" [emphasis added]

The applicants respectfully submit that the claims were last amended to recite:

"recombinant nucleic acid vectors encoding a conduction protein selected from the group Cx40, Cx43, and Cx45"[Amendment of August 31, 2001; emphasis added]

This amendment was introduced to align the claims directly with that which the examiner indicates the specification does provide guidance.

Applicants respectively submit that the identity, sequence, and purification of connexin genes are known, and the method for preparing vectors containing them is well known. Examiner is well aware of the teachings of Kanter (J. Mol. Cell Cardiol., 1994, 26, 861-868), Gourdie, et al. (J. cell Sci., 1993, 105, 985-991), and Fishman, et al., J Cell Biol, 1990, 111, 589-589). These references are directly discussed throughout Applicants specification. Applicants claims are fairly based as to the scope of connexins they are claiming – Cx40, Cx43, and Cx45. They are not claiming they discovered connexins. That teaching is in the art.

One of Applicants' inventions is directed to a system that allows people to know where to place conductive proteins in the heart. Another is to provide external controls and safety mechanisms to over-ride the control of the transfected genes. This is possible by the fact that the claimed catheter system contains cardiac mapping and pacing elements. The mapping element provides one skilled in the art the tools necessary to determine what area of cardiac tissue may need transfection (this is a problem not solved or identified in the art), and how to titrate and measure the effectiveness of their transfection by the ability to sense and measure any changes in cardiac conductivity by continued sensing of the myocardium (another problem not solved or identified in the art). Additionally, Applicants' invention provides a means for pacing by placing pacing electrodes in the catheter. Enabling the ability to pace the transfected tissue establishes external physical control mechanisms over the biological mechanisms. Not all problems have to be solved using only a "biological tool." This is what the Examiner seems to want. However, it appears that because Applicants have solved the very problem of the control of the transfected genes by different mechanisms, it is rejected out of hand.

As no surprise to Applicants, FDA is initially requiring implantation of pacemakers for human cell transplantation studies because of fears of possible rhythm irregularities. However, by providing the ability to use pacemakers at the delivery site to determine whether there is a rhythm irregularity, and if there is an irregularity, the ability to provide a safety mechanism to correct the problem both short term and long term is an important advancement in the art. This is a contribution of Applicants' invention.

Applicants' invention is ground breaking in that it provides a solution to the current problem in control of gene expression. Applicants' invention provides in part a pacing electrode that can be coupled to the physical hardware of a pacemaker that can correct problems that might appear as a result of transfection. In retrospect of the progress of the gene therapy field, people initially thought that you could just infuse a gene/vector into the cardiovascular system and that if you had the right biological transcription controls, all would be well. Based on an infusion type delivery system, the Examiner is correct in asking whether there are sufficient biological control mechanisms in a stand-alone infusion system. However, Applicants' invention is about using a catheter delivery system known in the art to deliver the genes directly to the heart, with the added feature of having a mapping electrode means to know exactly where in the heart to place the gene/vectors, and also providing a means for sensing whatever effect that the connexin genes are having, and if inappropriate rhythms develop, controlling the rhythm via a pacemaker via the ability to place a pacing electrode.

The Examiner also appears to contend that Applicants' only mode of transfection described is by electroporation:

> "In regards to the use of vectors such as viral or adenoviral vectors disclosed by the specification, the specification fails to provide essential teaching on the methods of delivery of genetic material from said catheter delivery device such that any electrical energy generated by the device would not adversely impact the ability of vectors to transduce cells in the cardiac tissue of damage the vector's stability and ability to transduce cells in the cardiac tissue or damage the vector's stability and ability to express the encoded transgene. The specification does not disclose to what extent the administration of an electric field from the applicant's device will effect the quantity, structural integrity, and biological properties of DNA or RNA delivered into the cells as a result of any increase in the permeation of the cell membrane. It is well known in the art that the administration of an electric field, such as in the use of electroporation, can result in a significant level (e.g. 40-80%) of cell lysis (e.g. See

> Weaver et at., US Patent 5,019,034, column 3, lines 44-64). The specification also fails to disclose the manner and ability of any genetic material to transduce cardiac tissue cells which have been damaged due to the use of a helical electrode which is screwed into the myocardium."

Applicants' specification on page 20, third full paragraph, discusses a number of transfection methods, one which includes electroporation. However, electroporation is but one transfection technique. Page 21, first full paragraph, specifically describes in vivo transfection of cells. The Examiner seems to be reading issues into the claims based on a false presumption that electroporation methodology is the only method described for transfecting cells. Applicants do intend to claim the use of their mapping catheter with any technique that is effective for transfection or transduction of the cardiac cells; however, the examiner seems to be saying all techniques are ineffective. Applicants also refer the Examiner back to discussion of US 5,797,870.

Applicants also draw the attention to portions of the specification where therapeutically effective amounts of adenovirus are discussed (page 25, at the bottom of the page) as providing a bolus of virus: "Where adenovirus vectors are used, the amount of recombinant nucleic acid molecule is preferably between 10^8 pfu and 10^{14} pfu, and most preferably between 10^9 pfu and 10^{12} pfu." The point of raising this matter is that if you compare the effective amounts used in the Maurice article, it was 5×10^{11} adeno-viral particles which is inside the preferred ranges given in the specification.

As to the last issue brought up by the Examiner in the last highlighted paragraph, the Examiner seems to be doubting the precedence of the US patent office in these matters for use of helical electrodes for transfection. Applicants do not think this is the case, but want to make sure that the Examiner understands that Applicants are claiming the use of mapping and pacing electrodes as part of the delivery system, and that the Examiner is not confusing this to be the same as using electrodes in an electroporation system. It is not.

The Examiner continues at length to document various problems that others have had, suggesting in essence that years of research will be required before any patentable advances in this area are forthcoming. In essence, the Examiner seems to believe that the patentees must

solve all problems for FDA approval before they will be granted a patent. It is respectfully indicated this is not the law. Second, Applicants inventive contribution is actually moving forward the scientific ability to have a successful gene therapy. First, Applicants use a local catheter delivery system (versus systemic infusion or injection of gene vectors). Second, Applicants' invention provides electrical sensing elements for mapping the conductivity of the heart prior to determining the specific location in the heart requiring transfection/transduction of the affected areas (again a significant contribution to the art). Third, Applicants have also provided a sensing means after transfecting, to know to what extent the transfected connexins are having, and, should some irregular conduction patterns occur, a mechanism for correcting that problem by having the ability to place the pacing electrodes for use of a pacemaker to take over control of the heart rhythm. One needs both sufficient connexin expression, and control of that expression. One means to control expression, if required, is by providing the ability to pace the heart.

One of Applicants' contributions to the art is that they provide a complete delivery system to effectively deliver genes to cardiac cells that affect conduction. The delivery systems of the art will be advanced by the presence of a conduction mapping system, so that baseline readings of the heart can be made as to where to effectively deliver these genes, as well as to gauge and monitor the effect of transfection/transduction of these genes. As the Examiner knows, there are well known groups of proteins that affect conduction in the heart – connexins, and ion channel proteins. Applicants have had applications covering these two aspects, which were filed on the same day, yet they are receiving almost irreconcilable reviews in prosecution. Applicants direct the Examiner to US 6,567,705 and US 6,665,563. The two issued patents were filed on the same day by the same inventors, using essentially the same systems for delivery. Applicants have had successfully issued patents relating to the use of their delivery system for ion channel proteins, yet the present application has received completely different treatment in relation to delivery of connexins.

The Examiner in the first full paragraph on page 6, seems to indicate that Applicants' specification provides no guidelines relating to the biophysical properties, or differences in tissue expression required for functional cardiac tissue:

> In addition to the lack of guidance concerning the identity of conduction proteins for use in the instant invention other than connexins, the identity of genetic material other than nucleic acid vectors, the effects of the claimed catheter delivery device on the ability of the cardiac tissue to take up foreign genetic material and the effects of the device on the ability of the genetic material to express any encoded protein as noted above, the specification fails to provide guidance as to the level of cardiac cell transformation, the types of cardiac cells transformed, and the level of expression of any conduction protein from any delivered genetic material that correlates with any effect on conduction in cardiac tissue in vitro or in vivo. The specification's sole disclosure of conduction proteins are members of the connexin family. At the time of filing, Kanter et al. discloses that the three members of the connexin gap junction family, Cx40, Cx43, and Cx45, have different biophysical properties, and that in combination they are believed to be important in the regulation of cellular coupling. Further, these proteins have regional differences in expression with the various cardiac tissues, such as the Purkinje fibers and ventricular myocytes, and they are not expressed in one-to-one ratios with any cardiac tissue (Kanter et al., page 861 columns 1-2, and page 866). The specification does not provide sufficient guidance that the expression of any level of any one connexin family member in any type of cardiac cell would have any effect on cardiac conductance. In view of the different biological properties of the connexin family members, the complex interactions between the family members that result in gap formation and cellular coupling, and the differential cellular distribution of the connexin family members, the skilled artisan would not have been able to predict whether the introduction of any connexin family member into any cardiac cell would result in any effect on cardiac conduction.

With due respect, Applicants draw the Examiner's attention to their specification starting at the bottom of page 22 and top of page 23 wherein they provide guidance to proper usage of these proteins for treatment of disease.

> "Determining the appropriate conduction protein genetic material, i.e., determining which connexin protein is appropriate, is dependent upon which protein is appropriate, is dependent upon the particular cardiac conduction disturbances diagnose. For example, if the cardiac conduction pathway is a heart block or bradycardia, in which conductance is slowed or non-existent, Cx43 or Cx40, the faster connexins, is preferably used. However, if the cardiac conduction pathway disturbance is tachycardia, in which conductance is too rapid, Cx45 is preferably used." [Specification, page 22-23]

In this passage Applicants teach where to use the appropriate connexin in a particular disease state. Similarly, Applicants discuss on page 9, at the bottom of the page, the use of the appropriate connexin in treatment of the appropriate disease and the location of the targeted tissue:

> "The specific gap junction protein chosen is dependent upon the nature of the identified problem. For example, where the conduction is slow or non-existent, such as in heart

block or bradycardia, introduction of Cx40 or Cx43 would enhance conduction. In contrast, introduction of the slower conducting Cx45 into the AV node and HIS tissues would result in the prevention of brady-tachy syndrome and tachycardia." [Specification, page 9]

Applicants' specification teaches those things that Examiner suggests it does not teach. Further, it is Applicants' invention that provides the mapping capabilities with the delivery system. Testing of the target tissue can be done before and after delivery. Note, in Applicants' specification they also teach leaving behind a pacing electrode after transfection. This enables continued monitoring of the tissue after transfection. The Examiner should be able to appreciate the significance of such a delivery system, that is novel, enabled, and inventive over the art.

Applicants respectfully request reconsideration of the amended claims in view of what is known in the art, and their contribution to the art, and respectfully submit that their claims are enabled and cover patentable subject matter.

(2) Claims Rejections – 35 USC § 103

The Examiner maintains her rejection of claims 1, 4-14, 20-25, 39-42 and 48-50 under 35 U.S.C. 103(a) over Mulier et al. in view of Leiden et al. and Kanter et al. Essentially the rejection was maintained since the Applicants' delivery system as claimed does not recite the limitation that the delivered genetic material has any effect on the cardiac tissue. As such, the Examiner found the combination of references cited provides motivation for using the catheter system taught by Mulier to deliver genetic material to cardiac tissue as taught by Leiden. Further, the skilled artisan would not consider the presence of tissue damage near the site of administration of genetic material as an obstacle to the transfection of nearby living cells. Therefore, as the limitation that the delivered genetic material must have a therapeutic effect on cardiac conduction is not recited by the instant claims, the Applicants' arguments are not found persuasive and the rejection is therefore maintained.

Applicants traverse in part, and submit amended claim 20. Applicants traverse on the issue that the combination of references actually teaches all elements of Applicants claimed

invention. Nowhere does this combination of references provide the essential mapping element or pacing element, or recognize that such feature is essential to have an effective transfection/transduction system.

As to the other part of the Examiner's rejection indicating that the invention does not recite a limitation that the delivered genetic material has any effect on the cardiac tissue. Applicants have amended Claim 20 so that the delivered material transfects the local cells, and that it provides a therapeutically improvement in cardiac conduction.

Applicants respectfully request reconsideration and removal of the present rejection under 35 USC §103 in view of the submitted arguments and amendments.

Conclusion

Finally, Applicants would like to again thank the Examiner for her guidance in this matter as well as for her willingness to discuss the issue regarding this applicaton.

The enclosed response attempts to narrow the issues under consideration and to put Claim 20 in a condition for allowance. Applicants respectfully request that the standing rejections to Claim 20 be withdrawn. Should Applicants not have succeeded in placing Claim 20 in a condition for allowance, Applicants respectfully request that their Request for Continued Examination be entered, so that in part their Supplemental IDS can be made of record and any remaining issues with regard to the prosecution can be handled. Finally, Applicants respectfully ask the Examiner for her support on their Reconsideration on their Petition to Revive.

Respectfully submitted,

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